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[A propos d'un cas d'intoxication chronique au Béryllium: considérations pathogéniques et valeur du «patch-test» pour le diagnostic]

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A CASE OF CHRONIC BERYLLIUM INTOXICATION: PATHOGENIC CONSIDERATIONS AND DIAGNOSTIC VALUE OF THE "PATCH-TEST"*

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ABSTRACT. We report a case of chronic beryllium intoxication in a forty-year-old technician who had fifteen years previously been exposed to the inhalation of beryllium oxide used in fluorescent tubes. The diagnosis was based upon the history, the radiological appearance and a positive patch-test with beryllium fluoride. Recent literature reports emphasize the great similitude of chronic beryllium intoxication and sarcoidosis, support the hypothesis that the tissue reactions induced by beryllium compounds are immunological reactions of the delayed type, and describe a carcinogenetic effect of beryllium in several animal species; if these reports are confirmed in man, it will be necessary to lower further the (already minimal) threshold limit value of beryllium.

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Introduction

Chronic berylliosis is a rare condition in Europe. In his work on sarcoidosis, Scadding (1967) reports that 7 cases have been observed in Great Britain since 1944; he adds two personal histories. In France, two cases were compensated by the National Health Insurance Fund for Salaried Workers during the period 1963 — 1967; a third case was recently reported by Macquet et al. (1967). Lastly, in Germany, 22 cases had been indemnified as of January 1, 1967. In Belgium, berylliosis has been recognized as an occupational disease since 1958* and, up to the present time, four claims have been presented to the Occupational Diseases Fund.

It is, therefore, not because of the practical importance or the frequency of this disease that we wish to report a case, but because the scientific interest in beryllium is still considerable for two reasons.

In the first place, the pathogenesis of berylliosis was recently studied from the clinical point of view (Pugliese, et al., 1968) as well as from the experimental point of view (Chiappino, et al., 1969). There is every reason to believe that the knowledge thus acquired will also find applications in the study of a much more frequently occurring disease, sarcoidosis, whose similarity to berylliosis is recognized.

Also, it is present acquired knowledge that beryllium exercises carcinogenic action in at least three animal species. Although the rare observations of human cancer associated with beryllium exposure do not allow one to extrapolate these experimental data to human clinical practice, neither does it seem permissible to ignore their potential value.

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*A. R. of September 5, 1958, appeared in the Monitor of September 26, 1958.

To these two questions of fundamental scientific interest, we wish to add a third of immediately practical import: does berylliosis still exist as an occupational disease in Europe, and, if so, are the methods for its detection adequate?

Clinical History. A 40-year-old man consults his treating physician in 1966, because he has felt more quickly winded for the last few weeks. He notices neither cough nor expectoration. On occasion his breathing is whistling, especially when he has a cold. There are no symptoms suggestive of cardiopathy; neither is there a family or personal history of allergy.

Physical examination reveals several sibilant rales at the level of both lung bases. Cardiac ausculation is negative, and there are no signs of cardiac decompensation. The blood pressure is 160/90 mm of Hg, the general state is good (67 kg for 1.71 m), and systemic examination reveals only bilateral varicosities of the calves and discrete thoracic scoliosis. The patient receives antibiotic treatment and bronchodilators. The sensation of shortness of breath persists, however, and a chest film taken three weeks later discloses the presence of a very dense cloud of micronodular and punctiform opacities 1 to 4 mm in diameter which almost completely covers the lung fields (Figure 1). Perhaps there also exists a slight accentuation of the right hilar indentation. Inasmuch as this picture was not necessarily consistent with the diagnosis of sarcoidosis, the possibility of pneumoconiosis was considered and occupational anamnesis was completed. The patient had begun to work at the age of 17, after completing secondary technical studies. Since then, and although he has always worked in the chemical industry, the only period during which he was exposed to pathogenic respiratory tract agents was from 1946 to 1950. At this time he worked in a laboratory which studied fluorescent tubes using beryllium oxide, inorganic tungsten, and arsenic phosphates. No precaution was taken to avoid the inhalation of this powder whose utilization was not definitively abandoned until four years later. Since 1950, the patient had performed mainly administrative duties, and was no longer exposed to respiratory tract irritants.

Figure 1. Radiograph, taken April 7, 1967, disclosing the presence of micronodular opacities in the two lung fields, particularly numerous at the apexes.

The routine hematologic examinations and urinalyses are normal. The pulmonary function tests (Table I, February, 1966) demonstrate neither involvement of the ventilating function or alveo-capillary diffusion at rest. A 100-watt effort sustained for five minutes, however, does provoke considerable hyperventilation with a marked pathologic ventilatory equivalent. There is also a slight metabolic acidosis.

No treatment was begun, given the absence of important clinical or functional alterations.

TABLE I

PULMONARY FUNCTION TESTS

	February 15, 1966	April 3, 1969
VC	3.98 l BTPS	3.56 l
FEV_1	3.10 l	2.16 l
RV	1.50 l	1.96 l
TLC	5.48 l	5.52 l
T_LCO*	22.9 ml/min/mm Hg	24.8 ml/min/mm Hg
PV_1**	80.7 ℓ/min	
RE**	47	
Blood Gases:		
At rest		
$PaCO_2$	35.8 mm Hg	29.5 mm Hg
PaO_2		74 mm Hg
pH	7.40	7.44
Satura.	96.5%	96%
HCO_3		19.8 meq/l

(Continued)

TABLE I

PULMONARY FUNCTION TESTS (Continued)

	February 15, 1966	April 3, 1969
Blood Gases (Continued):		
Effort		
$PaCO_2$	26.9	30 mm Hg
PaO_2		86 mm Hg
pH	7.35	7.41
Satura.	97%	96.6%
HCO_3		18.8 meq/l

*Inspiration of carbon monoxide alone.

**Minute volume and respiratory oxygen equivalent during 100-watt effort sustained for five minutes (heartbeat 160/min, oxygen uptake 1.21 l/min).

Figure 2.

Figure 3.

Enlargements of the lung apexes confirming the presence of numerous micronodular and punctiform opacities.

Between 1966 and 1968, we followed this patient regularly. His subjective and objective states remained unchanged. Enlargements of the lung apexes were taken during one of these examinations: the micronodular opacities were particularly pronounced (Figures 2 and 3).

Figure 4. Radiograph, taken December 13, 1968. The outline of the right hilum is perhaps more marked, and the micronodular opacities are perhaps somewhat more numerous than in the film of 1967 (Figure 1).

Figure 5. Tomogram of the hila: the possibility of right hilar adenopathy cannot be excluded with certainty.

New radiological and functional examinations were performed in December, 1968, and in April, 1969. Even though the comparison with the first initial films is rendered difficult by a difference in technique, it seems that the micronodules are presently more numerous and somewhat more dense than in 1966 (Figure 4). The tomograms confirm the impression of slight hypertrophy of the elements of the right hilum: the existence of adenopathies cannot be excluded with certainty (Figure 5).

From a functional point of view, there is a slight diminution of the vital capacity and the FEV_1, which respectively decrease to 89% and 70% of the initially measured values, whereas the residual volume seems to have increased slightly (+31%). CO transfer remains at the lower limit of the normal, and the arterial blood gases remain normal with a slight reserve for a fairly marked alveolar hyperventilation (Table I, April, 1969). The various laboratory tests disclose no anomalies; the blood total protein level is slightly elevated (8.8 g%), but the electrophoresis, alkaline phosphatase, and blood calcium level are within normal limits.

TABLE II

DIFFERENTIAL DIAGNOSIS BERYLLIOSIS — SARCOIDOSIS

		Berylliosis	Sarcoidosis
1.	Anamnesis	Occupational exposure and/or microclimate	Negative
2.	Hilar adeno-pathies (X-rays)	Rare	Frequent, above all in Stage I
3.	Kveim test	Negative	Positive
4.	Beryllium patch-test	Positive	Negative
5.	Localizations	Above all lungs, liver, spleen, lymphs nodes, kidney, skin	Idem, but further uveoparotid fever, bones, central nervous system
6.	Search for beryllium	Presence of beryllium ($\geq$0.1 µg/100 g) in lung tissue	Negative

Epicutaneous tests were performed using 0.01%, 0.1%, 1%, 2% and 5% beryllium fluoride concentrations, and were evaluated after seventy-two hours. The reactions were markedly positive at 0.1% and greater concentrations (Table III).

Industrial and Hygienic Aspects of Beryllium

Beryllium was discovered by Vanquelin in 1795 and was first called glucinium because of the sweet taste of its salts. It is a very fragile, gray-white metal whose atomic weight is 9.02. Its only source is the mineral beryl extracted in Brazil, Argentina, India, South Africa and Rhodesia. Its principal characteristics are its low density, its very high coefficient of elasticity, its good thermal conductivity, its elevated melting point (1,280° C) and its resistance to corrosion. These are the very particular properties which have brought about the use of beryllium in the aeronautic and space industries notably in the nose cones of rockets and gyroscopes. The alloys of copper and beryllium (most often about 2% beryllium) are utilized in the movable pieces of motors, springs, electric equipment and precision instruments. They are more resistant than copper alone, non-magnetic and do not produce sparks. Beryllium retards neutrons

TABLE III

RESULTS OF THE BERYLLIUM FLUORIDE "PATCH-TEST" FOR THE PATIENT REPORTED AND FOR 15 CONTROL SUBJECTS

	Case	BeF_2 Test*					Observations Read After	
		0.01%	0.1%	1%	2%	5%	48 hrs	72 hrs
1.	M — Berylliosis	—	+++	+++	+++	++++		X
2.	LL — Besnier's P.	—	—	—	—	—		X
3.	H — eczema of hands, undetermined origin		—	+++	+++	+++	X	
4.	D — eczema of hands, lithography worker		—	—	—	—	X	
5.	L — eleoconiosis	—	—	—	—	—	X	
6.	M — eczema by nickel allergy	—	—	—	—	+	X	
7.	G — eczema by allergy to chromium derivatives	—	—	—	—	++	X	
8.	T — eczema by allergy to chromium derivatives	—	—	—	—	—	X	
9.	B — eczema by allergy to chromium derivatives	—	—	—	—	+	X	
10.	M — eczema of undetermined cause	—	—	—	+	+	X	
11.	N — eczema of undetermined cause	—	—	—	—	—	X	
12.	S — eczema of undetermined cause	—	—	—	—	—	X	
13.	R — eczema of hands (allergic to nickel and dichromate)	— +++	— +++	— +++	— +++	+++ ++++	X	X
14.	L — eczema of hands (allergic to dichromate)	—	—	—	—	—	X	
15.**	H — eczema of hands (allergic to dichromate, to tetramethylthiuram disulfide)	—	—	—	—	—	X	
16.	S — eczema of hands (probable cause: cement)	—	—	—	—	—	X	

(Continued)

TABLE III
(Continued)

Interpretation of tests:

+ = erythema

++ = erythema and papula formation

+++ = vesicle formation (mini-eczema)

++++ = great vesiculation extending beyond original site of application

*Excipient used was vaseline

**This patient displayed a delayed reaction to all the concentrations six days after the tests.

without absorbing them because of its very low atomic number. Furthermore, it possesses a large scattering section (the probability is great that a neutron will encounter a beryllium nucleus). Since then, it has been used as a moderator in atomic reactors. Beryllium oxide whose melting point is high (2,550° C) is utilized in the ceramics industry and in X-ray diffraction tubes. The manufacture of fluorescent tubes containing beryllium oxide, though important in the past, has almost been completely discontinued.

Clinical Aspects

Beryllium is particularly toxic. The MAC* (American Industrial Hygiene Association Journal, 1969) is 0.002 mg per m^3 of air, which constitutes the lowest level of all the substances cataloged by the American Association of Governmental Hygienists.

The most toxic beryllium salts are the sulfate, the fluoride, the oxyfluoride (soluble) and the oxide (insoluble). Beryllium itself, but not its ore (beryl), has also caused intoxication. The possibility of non-occupational chronic intoxication poses an important public health problem. This intoxication was notably described

*Maximal Allowable Concentration: maximal concentration to which workers can be exposed for eight hours per day.

for housewives who cleaned their husbands' work clothes and for persons living in the vicinity of factories processing beryl (neighborhood cases).

From a clinical point of view, one classically distinguishes acute and chronic cases (of less than or more than one year's duration).

As opposed to chronic cases, the acute forms, up to the present time, appear to be the exclusive lot of industry. They would be provoked by soluble salts, whereas the insoluble salts would provoke more chronic lesions. The acute attack is characterized by lesions of the skin, the conjunctivae, and the respiratory tract mucosae. The cases of tracheobronchitis and pharyngitis most often recover in four to six weeks. The chemical pneumonia which is accompanied by toxic pulmonary edema is most often fatal in nature. Nonetheless, these cases are not too numerous: most often the patient afflicted with acute berylliosis complains only of retrosternal pain and a dry cough. These pains regress after several days, whereas the cough becomes worse and progressive dyspnea sets in. Anorexia, weight loss, subfebrile temperatures and a sensation of asthenia often accompany the respiratory symptoms. Radiological alterations are visible only after several days. One successively distinguishes diffuse infiltration followed by a progressive thickening of the bronchovascular interstitial tissue accompanied by nodules which are first fairly hazy, then become more and more clearly defined. The laboratory tests do not assist in clarifying the diagnosis. About 80% of the cases recover without sequels within one to six months. The lethality is about 7%, and 10% of the cases evolve towards chronicity. Treatment is totally symptomatic. It has yet to be proven that the corticosteroids diminish mortality, or that they avoid the trend toward chronicity.

Chronic berylliosis is more frequent than the acute form. In fact, it seems that the designation beryllium disease or beryllium intoxication (Hardy, 1962) would be more appropriate than that of berylliosis. In effect: a) the pathological involvement occurs not

only at the pulmonary level, but also at the level of the liver, the spleen, lymph nodes, kidneys and the teguments; b) certain biochemical alterations (hyperproteinemia, hypergammaglubulinemia, hypercalciuria, negative protein balance) seem to be especially frequent; c) the pathological lesions can disappear and the laboratory tests return to normal during the course of corticosteroid treatment.

It is evident that a number of these characteristics are common in sarcoidosis. The differential diagnosis of the two diseases is especially difficult, to the point that certain authors such as Scadding (1967) evade the problem by speaking of beryllium sarcoidis. Table II summarizes several characteristics which might help in the differentiation.

The symptoms of chronic berylliosis are not specific. The latent period following exposure can last, as in the case under consideration, for more than ten years (for example, Neu and Schreiber, 1967). Most often, the patient complains of dyspnea, a dry cough, and a loss of weight. Cyanosis, hippocratism, objective signs of pulmonary involvement and, in the ulterior stages, signs of right cardiac decompensation constitute the most important contributions of the clinical examination. Ten percent of the patients present renal lithiasis (hypercalciuria). Diffuse arthralgia and granulomatous skin lesions resembling those of sarcoidosis have been described sporadically. Somewhat granular opacities, which are in general less dense than those of the other pneumoconioses, are visualized on examination of the chest film. It also happens that these opacities meet from place to place. Nonetheless, pseudotumors, such as those encountered in silicosis, have never been described. No more than is the case for the other pneumoconioses, no parallelism exists between the clinical and radiological development. As is the case for other interstitial granulomatoses, the respiratory function is attacked by a restrictive type ventilatory deficiency with lowering of the compliance and an increase of the alveoloarterial oxygen gradient. The presence of beryllium in the lung tissue signals exposure to the metal, but does not prove that the latter has provoked intoxication. Moreover, there

is no correlation between the quantity of beryllium in the tissues and the extent or duration of the symptoms (Lieben, et al., 1963), and all persons exposed do not develop the disease. Furthermore, the epicutaneous tests (see further on), from the clinical and histological points of view, are of the hypersensitivity type and by the intratracheal injection of beryllium oxide, it has been possible to reproduce characteristic granulomatous lesions in the rat (Chiappino, 1969). Since then, it thus seems logical to attribute an important role to an immunological mechanism in the genesis of chronic berylliosis.

This conclusion is important because it allows one to induce the preventive as well as the curative treatment of berylliosis. In effect, if a hypersensitization mechanism whose threshold of intensity varies individually intervenes in the pathogenesis of berylliosis, it is possible that the permissible beryllium level in work areas should be reduced even more. Furthermore, these observations assure a more solid basis for corticosteroid treatment, and even immunosuppressors such as mercaptopurine which might act by reducing the number of monocytes responsible for the symptoms of inflammation (Page, et al., 1962).

Since the diagnosis of chronic berylliosis is often based in large measure on a positive test, in the absence of histological proof which is often difficult to furnish, this seems the opportune moment to conduct a more probing study of this disease. In a study involving 32 cases of chronic berylliosis, Curtis (1959) systematically performed a cutaneous beryllium test on these patients. Given the results obtained consistently in comparison to other chronic pulmonary conditions, he concluded that the patch-test is useful in the diagnosis of chronic berylliosis. He insists, however, that this test must not be considered as the only pathognomonic element of the condition and that it must be considered as one of a group of arguments (epidemiological as well as clinical: Stoeckle, et al., 1969) necessary to diagnose berylliosis when it has not been possible to demonstrate the presence of beryllium in the tissues.

The patch-test may, nonetheless, be of great importance in the diagnosis of pulmonary conditions, when it is a matter of ruling out the possibility of berylliosis and when one is confronted with a negative beryllium test.

Waksman (1959) is also of the opinion that the lesions of berylliosis correspond to hypersensitivity reactions; evidence of this state of hypersensitivity is demonstrated by the beryllium patch-test. The positive reaction to this test must be interpreted as a manifestation of hypersensitivity affecting all the tissues of the body.

Indeed, Curtis (1951) also studied cutaneous hypersensitivity to beryllium, and noted that 50% of the control subjects (persons who had never had previous contact with beryllium) nonetheless presented delayed cutaneous reactions to the patch-tests (spontaneous flare-up) occurring six to sixteen days after application of the beryllium salt to the skin. Of the different beryllium salts employed by Curtis for the patch-test, BeF_2 is considered particularly sensitizing.

It is necessary to perform tests at different BeF_2 concentrations, so as to avoid any primary irritation effects as well as delayed reactions.

This is what we have accomplished in comparing the cutaneous reactions of our case of berylliosis with a certain number of patients not presenting pulmonary conditions, but confirmed contact eczemas, either eczema of unknown etiology, constitutional eczemas, or even non-eczematous dermatoses (follicular eleoconiosis, for example).

From all these observations, relating to the specificity of the cutaneous BeF_2 test in chronic berylliosis, regrouped by comparing the results obtained in our patient with those of 15 cases of skin conditions (Table III), one can draw the following conclusions: 1. tardive, even violent reactions can occur in patients who have never had a "known" contact with beryllium; 2. increasing the BeF_2 concentration employed for the test, notably to 5%, increases the risk of

positive reaction, which, in our opinion, must be interpreted as the primary irritation (even though we might not have been able to furnish a histological argument).

While taking the fact into account that the cutaneous test is only additional proof in working up the diagnosis of chronic beryllosis, we believe that a patch-test performed at the 0.01% or 0.1% concentrations and positive after forty-eight hours would be of non-negligible diagnostic value.

Experimental Studies

A large number of studies have permitted one to attribute the pathogenesis of bony lesions (beryllium ricketts) to a selective inhibition of alkaline phosphatase (among others, Bamberger, et al., 1968). It is known, on the other hand, that the intravenous injection of beryllium provokes hypoglycemic episodes in animals by way of a mechanism which is still obscure. These observations, nonetheless, concern the administration of considerable quantities of beryllium by non-physiological routes, which would lead one to question their practical importance in human pathology.

The studies concerning the carcinogenic ability of beryllium are more interesting. Since Gardner and Heslington (1946) provoked osteosarcomas in rabbits by the intravenous injection of beryllium, their observations have been confirmed and extended by causing rats (alveolar adenocarcinoma, Reeves, et al., 1967a) and monkeys (A. J. Vorwald, 1962; Schepers, 1964) to inhale beryllium. Recent work has demonstrated that beryllium, like other carcinogenic agents such as aflotoxin and dimethylnitrosamine, accumulates in the nucleus of the intoxicated cells (Reeves, et al., 1967b), perhaps at the level of the phosphate groups of deoxyribonucleic acid (Truhaut, et al., 1968). Let us remember, in this regard, that Chèvremont and Firket had noticed, as early as 1952, that beryllium inhibits mitosis in cell cultures.

The very rare observations published up to the present time do not allow one to infer the existence of a causal relationship between beryllium exposure and human cancer. Such a relationship is notably suggested by the relatively high incidence of bronchial cancer in Rhodesia. On the other hand, the extraordinary frequency of this cancer in Great Britain in comparison with the United States, though tobacco consumption is comparable in these two countries, has led certain authors to condemn beryllium due to the Rhodesian tobaccos used in English cigarettes (Gold, 1967).

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